

The present invention, on the other hand, is in vivo process and concerns the use of mineral solutions which are extremely stable such that they can be autoclaved if required. The solutions are safe for application (including by injection) into the reproductive tract of an animal where they inhibit the generation, maturation, motility or viability of sperm without causing edema, pain, burning, etc.

This application is a continuation-in-part of application serial No. 230,582, for Minerals in Bioavailable Form, which issued on June 26, 1990 as U. S. patent No. 4,937,234. The solutions applied in the present process are described in U. S. patent No. 4,937,234 and, unlike prior art mineral solutions such as zinc tannate, do not injure the tissues (i. e., cause edema, pain, burning, etc.) when they are applied.

The broadest composition claim in U. S. patent No. 4,937,234 is as follows:

1. A pharmaceutically acceptable, bioavailable composition having a pH in the range from about 6 to 8 comprising a solution of a mineral gluconate salt and an amino acid capable of forming the solution, said mineral gluconate salt and amino acid being present in substantially equal molar amounts and at a concentration in the range from about 0.05M to 1.0M.

The present invention is directed to an aqueous solution of a mineral gluconate salt and an amino acid capable of forming the solution neutralized to a pH in the range from 6.0 to 7.5 for use in the reproductive tract of an animal to inhibit the generation, maturation, motility or viability of sperm when applied in an amount effective for that purpose.

The concentration of the mineral gluconate salt and amino acid is in the range from about 0.05M to about 2.0M. In a preferred embodiment (particularly for use in the

reproductive tract of a male), the mineral gluconate salt and amino acid are zinc gluconate and arginine, respectively.

In the present invention (as in U. S. patent No. 4,937,234), the mineral gluconate salt and the amino acid are present in substantially equal molar amounts. If excess amino acid is present (e. g., mineral gluconate salt and amino acid in a molar ratio 1:2), the solution will cause edema when it is injected.

#### The Prior Art

U. S. patent No. 4,684,528 to Godfrey was cited in the prosecution of the parent application (i. e., U. S. patent No. 4,937,234). In Godfrey, a peroral composition is described for use in treating colds and so forth. The amino acid is present in molar excess to the zinc (i. e., 2 to 20 moles of amino acid to 1 mole zinc salt) for the purpose of masking the disagreeable taste of some of the zinc salts used.

In U. S. patent No. 4,937,234, Applicant filed a Declaration Under Rule 132 showing that a molar excess of amino acid must be avoided and that the mineral gluconate salt and the amino acid must be present in substantially equal molar amounts. More particularly, examples 1 and 2 of the previous Declaration Under Rule 132 describe in vitro stability tests demonstrating that a solution having a zinc + amino acid molar weight ratio of 1:2 precipitates whereas a solution in accordance with U. S. patent No. 4,937,234 having a ratio of 1:1 is stable.

Example 3 (which is relevant to the subject application) describes an in vivo test demonstrating that a solution having a zinc + amino acid molar weight ration of 1:2 is not injectable into tissue whereas a solution with a ratio of 1:1 is injectable. Example 4 is another in vivo test showing that a solution with a 1:2 ratio cannot be orally

ingested without side effects whereas a solution with a ratio of 1:1 can be fed.

Applicant's solution delivers a higher concentration of zinc (10 to 100 mg per gram) than is possible with Godfrey's system (1 to 5 mg per gram). This is important inasmuch as an effective amount of the solution must be administered to the reproductive tissue undergoing treatment.

U. S. patent No. 4,956,385 to Eby discloses the administration of zinc salts (such as zinc lysinate) in the treatment of the common cold. It does not relate to a process of applying a solution of zinc gluconate neutralized with lysine or the like to the reproductive tract of an animal.

U. S. patent No. 4,339,438 to Fahim discloses the injection of a zinc tannate solution (pH 3.5) into the testes. Pursuant to this patent, a number of studies were made on the effect of intratesticular injection of zinc tannate in cattle and in dogs. In cattle, the animals evidenced testicular edema and difficulty in walking for about three days. In dogs, the animals licked and bit their testes, sometimes causing wounds in the skin of the scrotum. These adverse side effects made the process disclosed in U. S. patent No. 4,339,438 unacceptable to the farmer and pet owner.

In U. S. patent No. 4,339,438, applicant suggested that the zinc tannate solution be buffered to a pH from about 4.0 to about 6.5 to avoid discomfort to the subject. Unfortunately, when zinc tannate is neutralized with an alkaline salt, such as sodium chloride, edema is increased.

Based on applicant's earlier patent, there was no reason to believe that the edema could be avoided if a mineral gluconate salt (such as zinc gluconate) was substituted for

zinc tannate and if it was neutralized in the presence of an amino acid capable of forming the solution with the further requirement that the mineral gluconate salt and the amino acid be present in substantially equal molar amounts.

European Patent No. 0 132 821 to Ohashi et. al concerns the preparation of an aqueous solution containing lipid-soluble vitamin A, vitamin E and vitamin K. Hydrogenated lecithin and a neutral amino acid are added to stabilize the solution. The amino acids listed include glycine, alanine, beta-alanine, serine, threonine, valine, isoleucine, leucine, phenylalanine, methionine, histidine and taurine or their mixtures.

With the exception of histidine, the amino acids listed above are neutral. Histidine, on the other hand, contains a weakly basic imidazolium function and is borderline in its properties. At pH 6.0 more than 50 percent of histidine molecules possess a protonated or positively charged R-group, but at pH 7.0 less than 10 percent have a positive charge.

Vitamins are usually given orally or injected intravenously, intraperitoneally, subcutaneously and intramuscularly, but not into the male and female reproductive tracts. Applicant's methods as claimed herein, on the other hand, concern application of a solution to the reproductive tract and make use of an aqueous solution of a mineral gluconate salt neutralized in the presence of an amino acid capable of forming the solution to a pH in the range of 6.0 to 7.5 wherein the mineral gluconate salt and the amino acid are present in substantially equal molar amounts at a concentration in the range from about 0.05M to about 2.0M.

Chemical Abstracts 74(9):40226n and 95(23):198271s

show that zinc and calcium ions effect the motility and viability of sperm in vitro. Applicant's claims, on the other hand, are directed to the in vivo application of certain solutions of zinc gluconate which do not cause edema, pain, burning, etc.

Section 112 Issues

Applicant has addressed the Section 112 issues by amendment. For example, applicant has adopted the Examiner's suggestion that "comprising" be substituted for "by". The host and location being treated have been specified.

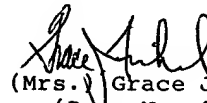
Summary

The compositions applied in the claimed processes are generally described in the parent application (of which the present application is a continuation-in-part) and are novel. As regards the present application, unlike other compositions containing zinc and calcium salts, they can be applied in the reproductive tract of an animal without causing edema, pain, burning, etc. while being effective to inhibit generation, maturation, motility or viability of sperm.

A copy of applicant's Declaration Under Rule 132 filed in the parent application is enclosed for the Examiner's reference.

In view of the above amendments and remarks it is believed that the claims are in condition for allowance. Reconsideration of the application and allowance of the claims are respectfully requested.

Respectfully submitted,




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